



Early View

Original article

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Safety of benzodiazepines and opioids in interstitial lung disease: A national prospective study

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ABSTRACT

Safety concerns are a barrier to prescribing benzodiazepines (BDZ) and opioids in Interstitial Lung Disease (ILD). We therefore examined association of BDZ and opioids on risk of admission to hospital and death.

We conducted a population based longitudinal cohort study of fibrotic ILD patients starting Long Term Oxygen Therapy in Sweden 2005-2014. Effects of BDZ and opioids on rates of admission to hospital and mortality were analysed using Fine-Gray and Cox regression whilst adjusting for potential confounders.

We included 1,603 patients (61% women). BDZ were used by 196 (12%), opioids by 254 (15%). There was no association between BDZ and increased admission. Treatment with higher vs lower dose BDZ was associated with increased mortality: (SHR 1.46, 95% CI 1.08 to 1.98) vs (SHR 1.13, 95% CI 0.92 to 1.38). Opioids showed no association with increased admission. Neither low dose opioids (<30mg/day morphine equivalent) (SHR 1.18 (95% CI 0.96 to 1.45) nor high dose opioids (>30mg/day morphine equivalent) (SHR 1.11 (95% CI 0.89 to 1.39) showed association with increased mortality.

This first ever study to examine associations between BDZ and opioid use and harm in ILD supports the use of opioids and low dose BDZ in severely ill patients with respiratory compromise.

Introduction

Interstitial Lung Disease (ILD) is the 40th most frequent cause of death [1] globally with a 52% increase in mortality in the last ten years.[1] Chronic breathlessness is experienced by almost all patients with advanced fibrotic ILD [2-5] and is one of the most common, burdensome and neglected symptoms affecting patients representing a major clinical management challenge. It has a devastating impact on patients' lives, severely limiting their well-being and quality of life, and that of their family, friends and caregivers. It results in high health, social and informal care costs, and is one of the most frequent causes of emergency hospital admission and attendance.[6] The recent UK National Institute Clinical Excellence guidelines recommend the use of BDZ and/or opioids for symptomatic management of breathlessness in idiopathic pulmonary fibrosis (IPF).[7] However, recent prospective studies showed that BDZ [8] and higher dose opioids [8, 9] were associated with increased hospital admissions and deaths in patients with COPD. In contrast, lower dose opioids (≤ 30 mg oral morphine equivalents/day), were not associated with hospitalization or mortality in this group.[8]

Data on the safety of BDZ and opioids in ILD are poor with only one relevant study [10] where treatment outcome of 22 patients with severe interstitial pneumonia who received opioids for 24 hours during end-of-life care were retrospectively examined. Twenty-two consecutive patients were retrospectively evaluated before and after continuous administration of opioids for 24 hours. All subjects died within 21 days; the mean survival period after opioid administration was 5.6 days. Six of the 22 patients (27%) died within 24 hours after opioids were initiated and hypercapnia was noted.

Ongoing concerns that these medications may cause adverse events, including respiratory depression, confusion, falls, and even premature death are cited as barriers for respiratory and

palliative care health professionals.[3] These concerns may cause reluctance to prescribe and use these medications, thus contributing to less than optimal symptomatic management with unnecessary suffering and hospital admissions. Data on safety may help inform day to day management and guide clinicians on optimal management of disabling symptoms.

We therefore estimated the association of BDZ and opioids on the risk of admission to hospital and death in patients with respiratory failure attributable to fibrotic ILD.

Material and methods

STUDY SUBJECTS

We included physician diagnosed pulmonary fibrosis patients aged 45 years or older starting LTOT between October 1, 2005 and December 31, 2014 (time period with available data on medications). Causes of pulmonary fibrosis included (but were not limited to) IPF, non-specific interstitial pneumonia. We excluded patients that had received lung transplantation. For patients who started LTOT more than once (n=24), only the most recent treatment episode was included in the analysis. Data were collected in Swedevox at baseline (start of LTOT); forced expiratory volume in one second (FEV₁) % of predicted, vital capacity (VC) % of predicted, FEV₁/VC, arterial blood gas tension of oxygen (PaO₂) and carbon dioxide (PaCO₂) whilst breathing air and oxygen, smoking status, body mass index (BMI) and World Health Organisation (WHO) performance status.

The study was approved by the Lund University research ethics committee (Dnr: 2016/846), the Swedish National Board of Health and Welfare, and the Data Inspection Board.

Individual patient consent was not required as the study used de-identified and un-re-identifiable data aggregated nationally.

STUDY DESIGN

This was a nationwide, prospective, population-based study of patients with physician diagnosed oxygen-dependent fibrotic ILD in the Swedish National Registry of Respiratory Failure (Swedevox).[11] Swedevox covers approximately 85% of patients starting long-term oxygen therapy (LTOT) nationwide since 1987.[11]

METHODS

We obtained data on co-morbidities and hospital admissions from the National Patient Register for inpatient and outpatient care for four years before baseline (complete data on hospitalisations since 1987 and on specialised outpatient care since 2001).[12] Data on all dispensed prescriptions during outpatient care after July 1 2005 were obtained from the Swedish Prescribed Drug Register. The medications of interest were categorised according to the Anatomical Therapeutic Chemical Classification System (ATC codes) as benzodiazepines (N05BA), weak opioids (N02AA59, N02AX02), strong opioids (N02A except weak), oral corticosteroids (H02A), azathioprine (L04AX01) and n-acetylcysteine (R05CB01).

ANALYSIS

Medication exposure was defined as at least one dispensed prescription during the 91 days before baseline. Exposure during follow-up was tabulated for patients classified as unexposed and exposed at baseline to evaluate whether baseline exposure was a good proxy for subsequent use during follow-up. Exposure to BDZ and opioids were coded dichotomously (treated vs. non-treated), continuously as the baseline dose, and categorised into lower and higher dose treatment. The baseline dose was calculated as the mean dispensed WHO defined

daily doses (DDD) per day during the 91 days before baseline. Lower dose treatment was defined as ≤ 0.3 DDD/day corresponding to ≤ 30 mg oral morphine equivalents/day, as this is the current evidence based dose range for opioid treatment for chronic breathlessness. [13, 14]. The same cut off was used for BDZ as it corresponded to the median dose in the exposed. Lower dose treatment defined as ≤ 0.3 DDD/day corresponded to ≤ 15 mg oral oxazepam equivalents/day.

BDZ (453 dispensed prescriptions) included oxazepam (87%), diazepam (6%) and alprazolam (5%). Opioids included the weak opioids (281 dispensed prescriptions) tramadol (53%), codeine (47%), and the strong opioids (351 dispensed prescriptions) oxycodone (49%), morphine (25%), fentanyl (9%) and dextropropoxyphene (9%).

Missing data were imputed for BMI (n=380), FEV₁ (n=623), VC absolute value (n=628) and percentage predicted (n=685), PaO₂ on room air (n=359), PaCO₂ on oxygen (n=366) and PaCO₂ on oxygen (n=249) using chained multiple imputation.[15] Outcome variables (days to death and days to hospitalisation) and covariates from the final models were used to estimate missing values. Number of imputations was set to 30 to reflect the amount of missing data [15] and imputed values were incorporated in the final models using Rubin's rules.[15] Covariates to be included in the final models were selected using subject matter knowledge.[8] Sensitivity analyses were conducted in people with complete data on all variables in the final models (complete case analysis) and excluding concurrent users of BDZ and opioids (n=59; 4%); see appendix A).

Associations with the rates of hospitalisation were expressed as sub-distribution hazard ratios (SHRs) estimated using Fine-Gray regression, which accounts for the competing risk of death.[16] For hospitalisations, the time under observation was from the first non-hospitalised day during LTOT until the date of first hospitalisation from all causes, with censoring at

withdrawal of LTOT, death, or study end (December 31, 2014). Associations with mortality were expressed as hazard ratios (HRs) and estimated using Cox regression. For mortality, the observation time was from the date of starting LTOT until the date of death from all causes, with censoring at withdrawal of long-term oxygen therapy, or study end. The assumption of proportional hazards for the medication effects was assured using Kaplan Meier plots and by splitting follow-up time to examine time-specific effects. We calculated 95% confidence intervals (CI) for all estimates. Statistical analyses were performed with Stata SE v13.[17] All data have been reported in line with STROBE guidance.[18]

RESULTS

In this population based longitudinal cohort study, there was no loss to follow-up. We included 1,603 patients (61% women) with fibrotic ILD starting LTOT. In the preceding 4 years there was a rheumatologic diagnosis (any) in 7.3%, pneumoconiosis in 3%, sarcoidosis in 1.7% and hypersensitivity pneumonitis was present in 1.5%. As shown in Table 1, BDZ were used by 196 (12%) patients, opioids by 252 (16%), and 59 (4%) patients were using both BDZ and opioids. Compared with non-users, patients taking BDZ or opioids were more likely to be female, have a lower FEV₁% of predicted, worse performance status, more hospitalisations in the 91 days prior to baseline and more comorbidities. Of note, there was no difference in their baseline lung function. Exposure to BDZ and opioids throughout follow-up was higher among patients with baseline exposure, and patients unexposed at baseline had low rates of exposed time during subsequent follow up (Table 2)

Table 1 Baseline characteristics according to treatment status of 1,603 patients with oxygen dependent fibrotic ILD.

	Benzodiazepine (n=196)	Opioid (n=252)	Unexposed (n=1,214)	P value
Age at starting LTOT, years	77.5 (8.2)	76.1 (8.9)	76.3 (8.8)	0.156
Women, n (%)	89 (45.4)	123 (48.8)	415 (34.2)	<0.001
FEV ₁ % of predicted*	66.3 (37.3)	67.0 (39.7)	71.6 (40.3)	0.106
VC % of predicted*	54.7 (34.2)	56.2 (35.6)	60.4 (34.7)	0.052
FEV ₁ /VC*	0.9 (0.3)	0.9 (0.3)	0.8 (0.4)	0.427
PaO ₂ breathing air*, kPa	6.5 (1.0)	6.6 (1.0)	6.6 (1.0)	0.441
PaCO ₂ breathing air*, kPa	5.3 (1.0)	5.3 (1.0)	5.1 (0.9)	<0.001
PaO ₂ breathing oxygen*, kPa	5.7 (0.9)	5.7 (1.0)	5.4 (1.0)	0.001
Smoking status, n (%)				
Never	61 (31.1)	66 (26.2)	338 (27.8)	0.797
Former	1 (1.0)	3(1.2)	9(0.7)	
Former/current	105 (53.6)	149 (59.1)	698 (57.5)	
Missing	30 (15.31)	37 (14.7)	178 (14.7)	
Body mass index (BMI)**, kg/m ²				
<18.5	10 (5.1)	12 (4.8)	35 (2.9)	0.579
18.5-24.9	107 (54.6)	143 (56.8)	707 (58.2)	
25-29.9	53 (27.0)	67 (26.6)	314 (25.9)	
≥30	26 (13.3)	30 (11.9)	158 (13.0)	
No (%) WHO performance status				
0-1	76 (38.8)	93 (36.9)	566 (46.6)	<0.001
2	54 (27.6)	70 (27.8)	350 (28.8)	
3-4	49 (25.0)	60 (23.8)	161 (13.3)	
Missing	17 (8.7)	29 (11.5)	137 (11.3)	
Median (IQ) number of hospitalisations within four years before baseline	4 (2-6)	4 (2-6)	2 (1-4)	<0.001
Median (IQ) number of hospitalised days out of the 91 days before baseline	14 (5.5 – 24)	15 (8 – 27)	11.5 (4 - 21)	<0.001
Percent of follow up time hospitalised (follow up time/ hospitalised days)	7.6 (2.3-20.3)	8.4 (2.6-19.8)	6.2 (2.1-16.8)	0;175
No (%) Cardiovascular diseases				
0	45 (23.0)	59 (23.4)	416 (34.3)	<0.001
1	3 (1.5)	3 (1.2)	58 (4.8)	
2	65 (33.2)	68 (27.0)	300 (24.7)	
≥3	83 (42.4)	122 (48.4)	440 (36.2)	
Comorbidity, n (%)				
COPD	50 (25.5)	67 (26.4)	234 (19.3)	0.010
Cancer	81 (41.3)	107 (42.5)	417 (34.4)	0.016
Depression/anxiety	43 (21.9)	33 (13.1)	37 (3.1)	<0.001
Diabetes mellitus	44 (22.5)	73 (29.0)	219 (18.0)	<0.001
Injury	33 (16.8)	54 (21.4)	154 (12.7)	<0.001
Osteoporosis	11 (5.6)	35 (13.9)	47 (3.9)	<0.001
Renal failure	18 (9.2)	25 (9.9)	65 (5.4)	0.007
Pulmonary hypertension	12 (6.1)	24 (9.5)	86 (7.1)	0.315

GERD	12 (6.1)	18 (7.1)	37 (3.1)	0.003
Benzodiazepine, n (%)				
Higher (>15mg oral oxazepam equiv/day)	65 (33.2)	27 (10.7)	-	
Low (\leq 15mg oral oxazepam equiv/day)	131 (66.8)	32 (12.7)	-	
Opioid, n (%)				
Higher (>30mg oral morphine equiv/day)	33 (16.8)	122 (48.4)	-	
Low (\leq 30 mg oral morphine equiv/day)	27 (13.8)	130 (51.6)	-	
Oral corticosteroids, n (%)	107 (54.6)	135 (53.6)	603 (49.7)	0.284
Azathioprine, n (%)	8 (4.1)	13 (5.2)	89 (7.3)	0.142
N-Acetylcysteine, n (%)	81 (41.3)	76 (30.2)	372 (30.6)	0.010

Data presented as means (standard deviation) unless otherwise stated. P value calculated using anova, kwallis or X²

*summary statistics for imputed data applying Rubin's combination rules, % missing: FEV₁ % of predicted (42.4%); VC % of predicted (42.7%); FEV₁ (38.9%); VC (39.2%); PaO₂ breathing air (22.4%); PaCO₂ breathing air (22.8%); PaO₂ breathing oxygen (15.5%). Immunosuppressive drugs (including mycophenolate) used by 5 patients at baseline.

**Missing BMI (31.1%) imputed into category 18.5-24.9

Table 2 Exposure to benzodiazepines and opioids in 1,603 patients with fibrotic ILD.

	Benzodiazepines	Opioids
Exposed at baseline		
Total	196	252
Low dose	131 (66.8)	130 (51.6)
Higher dose	65 (33.2)	122 (48.4)
Median (IQR) dose at baseline (DDD/day)	0.2 (0.1-0.4)	0.3 (0.1-0.5)
Exposed at baseline but unexposed during follow-up	51 (26.0)	77 (30.6)
Median (IQR) exposure during follow-up (% of time)	83 (0-100)	63 (0-100)
Medication-naïve (unexposed) in preceding 12 months*	55 (29.3)	59 (25.0)
Not exposed at baseline		
Total	1,407	1,351
Unexposed at baseline but exposed during follow-up	429 (30.5)	401 (29.7)
Median (IQR) dose during follow up (DDD/day)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Median (IQR) exposure during follow-up (% of time)	0 (0-16)	0 (0-10)
Medication-naïve (unexposed) in preceding 12 months*	1,199 (92.7)	1,034 (83.1)

*Among patients with at least 12 months medication exposure data (n=1,481). Figures are numbers (percentages) unless stated otherwise

Admission to hospital

Overall, treatment with BDZ had no significant association with increased rates of hospitalisation, SHR 1.21 (95% CI 1.00 to 1.46). Further analysis of low dose BDZ (≤ 0.3 DDD/day; SHR 1.19, 95% CI 0.95 to 1.49) and high dose BDZ (> 0.3 DDD/day; SHR 1.27, 95% CI 0.92 to 1.73) showed no association with hospitalisation. Opioids were not associated with hospitalisation, SHR 1.14, 95% CI 0.96 to 1.35. Low dose opioids (≤ 0.3 DDD /day; SHR 1.21, 95% CI 0.96 to 1.52) and higher dose opioid treatment (> 0.3 DDD /day; SHR 1.08, 95% CI 0.86 to 1.35) did not increase the rate of admission. There were no dose-response relations (Table 3 and Figure 1).

Mortality

In general, opioids were associated with increased mortality, SHR 1.18 (95% CI 1.01 to 1.38). However, a detailed analysis of the adjusted risks for each dose level showed that neither low dose opioids (SHR 1.22; 95% CI 0.99 to 1.50) nor higher dose opioids (SHR 1.11; 95% CI 0.89 to 1.39) were associated with increased mortality. BDZ treatment was related to mortality (HR 1.21; 95% CI 1.01 to 1.44) and this was dose dependent. Low dose BDZ was not associated with mortality (SHR 1.13, 95% CI 0.92 to 1.38) whereas higher dose BDZ was associated with increased mortality (SHR 1.46, 95% CI 1.08 to 1.97; (Figure 2 and 3). As a further predictor, a WHO performance status of 3 or 4 was associated with increased mortality (SHR 2.00; 95% CI 1.67 to 2.38).

Table 3 Benzodiazepine and opioids and adjusted hazard ratio of admission to hospital and mortality in 1603 patients with LTOT dependent fibrotic ILD.

	Adjusted hazard ratio (95%CI)*	
	Admission	Mortality
Benzodiazepines:		
Untreated	1	1
Low dose	1.19 (0.95 to 1.49)	1.13 (0.92 to 1.38)
Higher dose	1.27 (0.92 to 1.73)	1.46 (1.08 to 1.97)
Opioids:		
Untreated	1	1
Low dose	1.21 (0.96 to 1.52)	1.22 (0.99 to 1.50)
Higher dose	1.08 (0.86 to 1.35)	1.11 (0.89 to 1.39)
Covariates		
Age (years)	0.98 (0.98 to 0.99)	1.02 (1.01 to 1.03)
Male	1.05 (0.93 to 1.19)	1.41 (1.24 to 1.60)
VC % of predicted	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)
FEV ₁ /VC	1.07 (0.94 to 1.22)	0.99 (0.89 to 1.11)
PaO ₂ breathing air	1.00 (0.93 to 1.07)	1.00 (0.94 to 1.07)
PaCO ₂ breathing air	0.95 (0.84 to 1.07)	0.89 (0.79 to 1.00)
PaO ₂ breathing oxygen	0.99 (0.88 to 1.10)	0.99 (0.89 to 1.11)
BMI		
<18.5	1	1
18.5-24.9	1.26 (0.86 to 1.85)	0.72 (0.52 to 0.99)
25-29.9	1.30 (0.87 to 1.92)	0.70 (0.50 to 0.97)
≥30	1.28 (0.85 to 1.93)	0.54 (0.38 to 0.77)
WHO performance status		
0-1	1	1
2	1.09 (0.95 to 1.25)	1.48 (1.29 to 1.70)
3-4	0.78 (0.63 to 0.96)	2.00 (1.67 to 2.38)
Missing	1.04 (0.86 to 1.26)	1.49 (1.22 to 1.81)
N of cardiovascular diseases		
0	1	1
1	1.11 (0.85 to 1.47)	1.03 (0.76 to 1.41)
2	1.05 (0.90 to 1.22)	0.99 (0.85 to 1.16)
≥3	1.04 (0.89 to 1.21)	1.05 (0.90 to 1.23)
Comorbidity		
Cancer	1.15 (1.02 to 1.30)	0.85 (0.75 to 0.96)
Depression/anxiety	0.79 (0.60 to 1.05)	1.08 (0.82 to 1.41)
Diabetes mellitus	0.95 (0.82 to 1.10)	1.04 (0.90 to 1.20)
Injury	1.05 (0.90 to 1.24)	1.10 (0.93 to 1.29)
Osteoporosis	1.03 (0.80 to 1.33)	0.83 (0.64 to 1.09)
Renal failure	0.83 (0.61 to 1.13)	1.50 (1.19 to 1.90)
Pulmonary hypertension	0.88 (0.68 to 1.14)	1.10 (0.86 to 1.41)
GERD	1.15 (0.85 to 1.56)	0.85 (0.62 to 1.17)
N hospitalisations within 4 years before baseline	1.05 (1.02 to 1.07)	0.99 (0.97 to 1.01)
N hospitalised days within the 91 days before baseline	1.00 (1.00 to 1.01)	1.00 (1.00 to 1.01)

*Model adjusted for all variables in the table as well as smoking status, and use of corticosteroids, azathioprine and NAC

Sensitivity Analyses

A complete case analysis was carried out for comparison and is shown in Appendix A.

Observed differences between the models are minor, however, in the complete case analysis, higher dose BDZ are no longer a significant predictor of mortality and higher dose opioids become a significant predictor of admissions. Given the much smaller sample in the complete case analysis, and the bias introduced by excluding those cases with missing data, the models presented in table 3 using imputed data are more robust. When removing concurrent users of both BDZ and opioids, findings were similar as to in the main analysis (Appendix A).

Discussion

In this nationwide, population-based study using prospectively collected, linked, routine clinical data, the main findings are that treatment with opioids were not associated with increased risk of admission to hospital or death in patients with oxygen-dependent fibrotic ILD. Treatment with BDZ was not clearly associated with the rate of hospital admission but was associated with increased mortality at higher doses.

Internationally, no medication is licensed for chronic breathlessness, but emerging evidence in other disease groups such as COPD supports regular, low dose morphine as safe and efficacious. This is the first study examining safety data for BDZ or opioids in ILD.

Ekström *et al* [8] studied 2,249 patients with oxygen-dependent COPD in Swedevox and found that lower dose opioids were not associated with increased admissions or deaths.

However, higher doses of opioids and all doses of BDZ were associated with increased admissions and increased mortality. This is in contrast to Vozoris *et al* [9] who also conducted a registry-based study and found that people with COPD prescribed opioids who had an incident opioid prescription had a 30-day mortality risk of 1.9% compared with 1.1% without an opioid prescription after propensity score matching; an absolute difference of 0.8%. However, it was not clear that the observed risk difference was due to opioid medication as there were many potential confounders.[19] In contrast, our study does not show an association between opioids at either low or high dose and harm.

BDZ reduce the sensation of breathlessness through decreasing the anxiety associated with breathlessness.[20] Our data shows that depressed/anxious patients were much more likely to be prescribed BDZs and opioids. Ekstrom *et al* found that all doses of BDZ were associated with increased admissions and increased mortality in their COPD patients. Our study also does not clearly show an association between BDZ use and hospital admission but does suggest an association with mortality. As our patient group included palliative care patients, a

possible explanation, at least partly, for this is that there was increased BDZ use at the end of life for management of anxiety-related breathlessness as recommended by clinical guidance.[20] Supporting this, worse performance status was also associated with increased mortality.

Our data show that the use of BDZ and opioids in fibrotic ILD was low (12% and 15% respectively) and that opioid prescribing is much lower than that found in a retrospective review of fibrotic ILD patients in the last year of life in the UK (18% and 49% respectively).[2] In addition, our medication-naïve group (Table 2) was much larger than that found by Ekstrom *et al.*[8] This suggests that BDZ and opioids when used, are not being used until disease is advanced and patients are oxygen dependent. This is despite universal breathlessness at presentation.[5, 21] This is potentially a group of patients that may benefit from holistic management of symptomatic chronic breathlessness (which is not focussed on oxygen saturations) including the use of BDZ and opioids earlier in the disease process.

A recent ILD position statement stressed the importance of delivering early and effective palliative care.[22] This study provides novel data on the safety of BDZ and opioids in oxygen dependent ILD and may allay fears of clinicians who have been reluctant to prescribe these medications. Higginson *et al* [23] linked 14 years of death registration data and showed that 45,712 people died of ILD in England between 2001-2014 with increases of 9.2% annually. Importantly, 70% of these deaths were in hospital. Improvements in breathlessness management may decrease patient admissions and deaths and improve the quality of life of ILD patients and carers.

Patients with Interstitial Lung Disease have a wide range of diagnoses and prognoses. Many patients can live many years with their diagnosis and some are responsive to treatments.

However, a subset of patients with progressive fibrotic ILD such as IPF have a short disease trajectory and a similar prognosis to people with lung cancer.[24] It is important to differentiate fibrotic disease in the early stages when the disease is potentially responsive to therapy.[25] However, when the disease is advanced and irreversible, this becomes less important and the focus should be on symptom control.

IPF is one of the most common ILDs. Recent European data reflects worldwide data that IPF is more common in males (approx. 60:40) and this prevalence increases with age.[26, 27] Our data at baseline reflect a higher proportion of women (61%). On analysis, there were a higher proportion of men in the unexposed group compared with the exposed group, indicating that women with fibrotic ILD are more likely to be prescribed BDZ and opioids. In COPD, the physiologic changes affect women and men differently in terms of symptoms and quality of life. For a similar degree of physiologic impairment, women experience more severe breathlessness and worse health status.[28] Women with COPD also demonstrate higher levels of anxiety and depression and worse symptom-related quality of life than their male counterparts.[29] Comparable data in ILD are lacking and warrant further investigation to enable symptom management to be tailored to individual needs.

Strengths and limitations of the study

The present findings pertain to patients with severe oxygen dependent fibrotic ILD. This is a strength of the study as this population with advanced disease and respiratory compromise may be more likely to experience adverse events. Thus, the absence of a clear association for opioid use and low dose BDZ with hospitalisations and mortality is most informative in this population. As only 60 patients had concurrent BDZ and opioid use, we were unable to

analyse the association of concurrent medications and we were also unable to examine the effect of short-acting vs long-acting drug forms. This was a convenience cohort, not necessarily powered to answer a question on safety and we did not have an a priori power calculation. Therefore, we cannot exclude an effect that may be clinically significant. However, a lack of association of harm is informative. These data are comprehensive but limited to Sweden. Data on diagnostic procedures were unavailable therefore we are unable to present individual fibrotic ILD diagnoses. However, in a previous validation of fibrotic ILD diagnoses in the Swedevox register which included review of medical records, 80% were classified as probable IPF.[30] Similar selection criteria were used in the present study.

Recent development of IPF registries worldwide [31, 32] have enabled the documentation of important parameters including type of ILD, lung function, radiology, quality of life, ongoing treatments, follow-up and outcomes such as death and lung transplantation. This will make analyses of worldwide data related to ILD easier going forward. This study highlights that registry data needs to be complemented with detailed pharmacovigilance randomized controlled trials quantifying adverse events and benefits to further direct clinical care.

This is the first ever study to examine associations between BDZ and opioid use and harm in ILD patients. The evidence generated indicates that opioids are not associated with harm in people with severe oxygen-dependent ILD. Higher dose BDZ may be associated with increased mortality. The possibility of true causal effects, however, needs to be validated by randomised controlled trials.

By providing valuable data on the safety of BDZ and opioids, this study may allay fears of clinicians who have been reluctant to prescribe these medications. This study supports the use of opioids and low dose BDZ to manage breathlessness in severely ill ILD patients with respiratory compromise- patients who have significant symptom burden which impacts every

part of patients' and carers' lives. Increased prescribing may lead to improved symptom control and quality of life for this patient group.

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Figure 1 Forest plot of BDZ and opioids and admissions

Figure 2 Forest plot of BDZ and opioids and mortality

Figure 3 CIF plot of BDZ on mortality

Study

ID

Benzodiazepines

All doses

Low dose

High dose

Opioids

All doses

Low dose

High dose

.6

.8

1

1.2

1.4



Study

ID

Benzodiazepines

All doses

Low dose

High dose

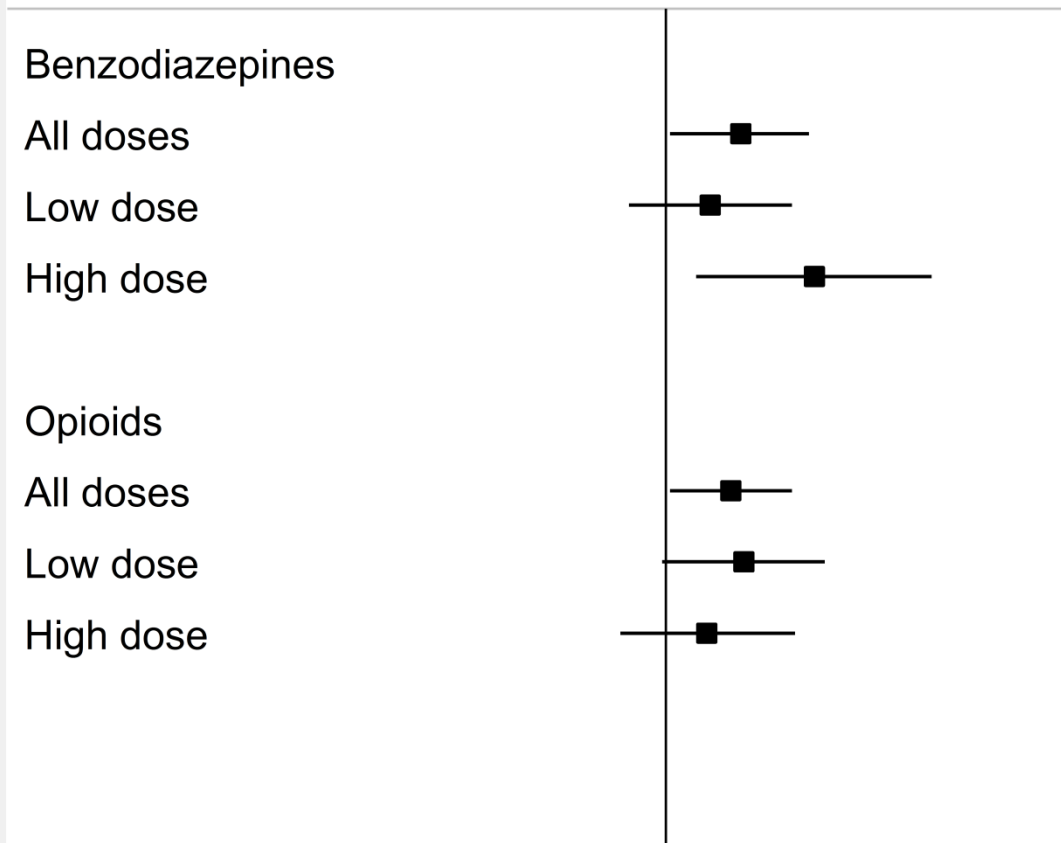
Opioids

All doses

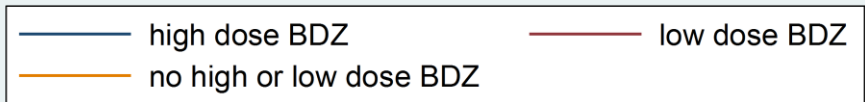
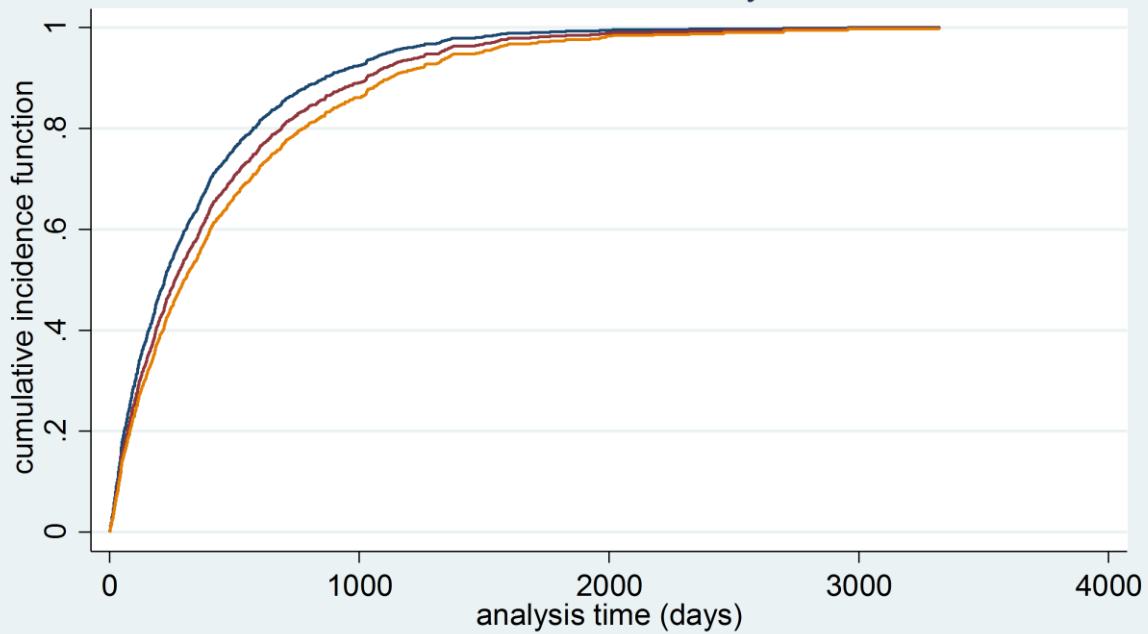
Low dose

High dose

.6 .8 1 1.2 1.4



BDZ on mortality



Supplementary file: sensitivity analysis

Table 1: Complete case analysis: BDZ and opioid adjusted risk of hospital and mortality in 682 patients with oxygen dependent COPD and complete data

	Adjusted hazard ratio (95%CI)	
	Admission	Mortality
Benzodiazepines:		
Low dose	1.16 (0.81 to 1.64)	1.25 (0.92 to 1.70)
High dose	1.38 (0.79 to 2.41)	1.62 (0.98 to 2.67)
Opioids:		
Low dose	1.18 (0.82 to 1.68)	1.11 (0.74 to 1.66)
High dose	1.51 (1.07 to 2.14)	1.34 (0.97 to 1.85)

Table 2: Excluding concurrent users: BDZ and opioid adjusted risk of hospital and mortality in 1544 patients with oxygen dependent COPD (using imputed data), excluding patients with concurrent BDZ and opioid use (n=59)

	Adjusted hazard ratio (95%CI)	
	Admission	Mortality
Benzodiazepines:		
Low dose	1.26 (0.98 to 1.62)	1.07 (0.83 to 1.36)
High dose	1.37 (0.94 to 2.01)	1.62 (1.11 to 2.34)
Opioids:		
Low dose	1.24 (0.96 to 1.61)	1.23 (0.98 to 1.55)
High dose	1.15 (0.90 to 1.48)	1.08 (0.84 to 1.39)

Adjusted hazard ratios with 95% confidence intervals, adjusted for BDZ and opioid dose, age, gender, VC % of predicted, FEV1/VC, PaO2 breathing air, PaCO2 breathing air, PaO2 breathing oxygen, Smoking status, BMI, WHO performance status, number of cardiovascular diseases, comorbidities, previous hospitalisations 4 years before baseline, number of hospitalised days 91 days before baseline, oral corticosteroids, azathioprine and NAC.